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The involvement of Fc gamma receptor gene polymorphisms in Kawasaki disease

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Summary

Kawasaki disease is an acute febrile syndrome in infancy, characterized by vasculitis of medium-sized arteries. Without treatment the disease can lead to coronary artery lesions (CAL) in approximately 25% of the children. Therapy consists of intravenous immunoglobulins (IVIG), leading to a decrease of complications to 5–16%. Little is known about the working mechanisms of IVIG. In this study we evaluated the involvement of Fcγ receptors (FcγRs) in Kawasaki disease by the determination of the frequency of known single nucleotide polymorphisms (SNPs) in the genes coding for the FcγRs and compared this with frequencies in a cohort of healthy controls. There was no difference in the distribution of the functionally relevant genotypes for FcγRIIa-131H/R, FcγRIIb-232I/T, FcγRIIIa-158 V/F and FcγRIIIb-NA1/NA2 between the patient group and the healthy controls. Furthermore, there were no polymorphisms linked to the disease severity as indicated by the absence or development of CAL during the disease. Altered transcription or expression of FcγR on specific cell types of the immune system may still play a role in susceptibility and treatment success, but at a level different from the functional SNPs in FcγR genes tested in this study.

Keywords: Fc gamma receptors, intravenous immunoglobulin, Kawasaki disease, single uncleotide polymorphism

Introduction

Kawasaki disease is an acute febrile syndrome in infancy, which is characterized by vasculitis of mainly the medium-sized arteries. Because there is no specific test to diagnose the disease, diagnosis is made on clinical criteria [1,2].

The incidence of Kawasaki disease is 5–17 per 100 000 in Europe and the United States, mainly in children under the age of 5 years. For unknown reasons the incidence in Japan is 135 per 100 000 [3]. In approximately 25% of the children vasculitis will lead to coronary artery lesions (CAL) as detected by echocardiography, showing this to be the leading cause of acquired heart disease in children.

Therapy consists of a single high dose of intravenous immunoglobulins (IVIG, 2 g/kg) infused in 8–12 h and aspirin. This therapy decreases complications to 5–16% [4,5]. To date, little is still known about the working mechanisms of IVIG. One of the proposed mechanisms of action of IVIG depends on the functional interaction with Fcγ receptors (FcγRs). FcγRs are receptors for the constant region of immunoglobulins (the Fc region) [6]. They play an important role in the immune response against invading microorganisms. FcγRs enhance the identification and destruction of nocuous material, foreign as well as endogenous, by opsonization. Hereby they form the link between the humoral and cellular parts of the immune system, as well as a crucial link between innate and adaptive immunity [7].

The group of FcγRs comprises three different classes: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16). Depending on their expression on effector cells, FcγR exert different effects. For example, on phagocytes they mediate phagocytosis, endocytosis, antibody-dependent cellular cytotoxicity (ADCC) and induction of respiratory burst [6]. Apart from expression, a 100-fold difference in IgG-binding affinity exists. FcγRI is considered as high-affinity receptor and types II and III [8,9] as low-affinity receptors. Of these receptors, FcγRII is the most widely distributed class and is expressed on most types of blood cells [6,10]. FcγRII is the only FcγR member with its own signalling motif and contains, depending on the isoform, either an immunoreceptor tyrosine-based activation motif (ITAM) or an immunoreceptor tyrosine-based inhibitory motif (ITIM). FcγRIIa contains an ITAM motif and is therefore an activation receptor, whereas FcγRIIb contains an ITIM motif and acts as an inhibitory

receptor [6]. In FcγRIIa, an important functional single nucleotide polymorphism (SNP) has been identified, resulting in an arginine (R) or a histidine (H) at amino acid position 131 [11]. These polymorphic variants have been shown to interact differently with IgG subclasses; FcγRIIa-H131 binds human IgG_2, whereas FcγRIIa-R131 does not [10,11]. A polymorphism in the transmembrane domain of FcγRIIb has been identified to affect the inhibitory activity of the ITIM motif [12]. Genetic polymorphisms affecting IgG-subclass binding also exist in *FCGR3A* [13] and *FCGR3B* genes [14]. As a result of such SNPs, the FcγRIIIa-V158 variant has a higher affinity for IgG_1 and IgG_3 than the FcγRIIIa-F158 variant [13]. Allelic variation in FcγRIIIb is comprised of differences in four amino acids, referred to as neutrophil antigen 1 (NA1) and NA2 [13]. FcγRIIIb-NA1 internalizes IgG_1- or IgG_3-opsonized particles more efficiently than FcγRIIIb-NA2 [14].

During recent years an increasing number of papers has been published on the linkage of various polymorphisms in the *FCGR* genes and a variety of diseases [15–25]. These diseases belong to the groups of infectious as well as autoimmune diseases. As it is generally accepted that Kawasaki disease is triggered by an infectious agent in genetically predisposed children, we investigated the possible association of functionally relevant SNPs in the *FCGR2* and *FCGR3* genes and Kawasaki disease. We hypothesized that this association could be true either for the entire cohort of Kawasaki disease patients (certain polymorphisms as a risk factor for increased susceptibility for Kawasaki disease) or for a subgroup of patients (as a risk factor for coronary artery damage and therapy failure).

Subjects and methods

Study population

In this study we included 167 patients with Kawasaki disease from our region, using the criteria for diagnosis and echocardiographic scoring according to the guidelines of the Kawasaki Disease Research Committee in Japan from 1984. Coronary artery dilatations with a diameter > 3 mm or > 1·5 times the adjacent vessel diameter were scored as aneurysmatic lesions. Standard therapy consisted of a single IVIG infusion (2 g/kg in 8–12 h) in combination with oral aspirin (80–100 mg/kg divided in four equal doses). A second IVIG infusion was administered when clinical symptoms (i.e. fever) persisted for 72 h or when echocardiographic findings were compatible with a progression or recurrence of CAL or the presence of a giant aneurysm (diameter > 8 mm). Echocardiographic findings were recorded before or shortly after the first IVIG infusion; follow-up was at 1–3-week intervals during the first 2–3 months, with an increase in frequency of visits depending on the presence, development or persistence of CAL. Healthy Caucasian blood donors ($n = 239$) were recruited as controls. The controls were unrelated and lived in the same region as the Caucasian Kawasaki disease patients included in this study. Informed consent was obtained from all participants or parents/caregivers of the participants in the study. The study was approved by the medical ethical committee of the Academic Medical Centre (AMC), Amsterdam, the Netherlands.

Genotyping

We isolated the DNA from blood using the Puregene DNA isolation kit (Biozym; Hess, Oldendorf, Germany).

Primers and conditions for the polymerase chain reactions (PCR) for assessing the *FCGR* polymorphisms

The primers for the PCR reactions used to assess the *FCGR* polymorphisms are listed in Table 1. *FCGR2B* genotyping for the FcγRIIb-232I/T isoforms was performed by direct sequencing, using the same 2B/2C intron 4 primer used in PCR and an internal 2B/2C intron 5 reverse primer. The PCR condition for *FCGR2B* is as follows: the target DNA was amplified by 40 cycles of 94°C for 30 s, 60°C for 45 s and 72°C for 45 s, stimulated and heated lid (standarized condition in the DNA auplification of the PCR–product) at 105°C; for *FCGR2A* we used an allele-specific PCR with two internal control primers (Table 2), with conditions as follows: one cycle of 5 min 95°C, 2 min 58°C and 1 min 72°C, thereafter 10 cycles of 1 min 95°C, 2 min 58°C, 1 min 72°C and a final extension step for 5 min at 72°C. For *FCGR3A* the target DNA was amplified by one cycle at 95°C for 5 min, at 56°C for 1 min and at 72°C for 1 min, 30 cycles at 95°C for 1 min, at 56°C for 1 min and at 72°C for 1 min, and an elongation step at 72°C for 5 min. Direct sequencing was performed on the PCR product, using the same primers. For *FCGR3B* we used an allele-specific PCR with two internal control primers (Table 2). The amplification started with one cycle of 5 min at 95°C (denaturation), 1·5 min at 60°C (annealing), 2·5 min at 72°C (extension) and was followed by 10 cycles in which the denaturation time was reduced to 1 min. Subsequently, 24 cycles were performed consisting of 1 min at 95°C, 1 min at 57°C and 1 min at 72°C and finally one cycle of 1 min at 95°C, 1 min at 57°C and 5 min at 72°C.

Statistical analysis

Differences between Kawasaki patients and healthy controls in the frequencies of the polymorphisms for the various *FCGR* genotypes as well as of all possible combinations of the subtypes, were tested with χ^2 tests. The relationship between the *FCGR* subtypes as well as several known risk factors and development of CAL (yes/no) was studied with logistic regression analysis. All variables associated

Table 1. Primers for FCGR genotyping.

Primer name	Primer sequence
2B/2C intron 4 forward primer	5′-TGG GAC AAG GAG AGT ACT GCC TGT C-3′
2B intron 6 reverse primer	5′-TTT GAG CCC CAG CCA TCC TCC CAC T-3′
2B/2C intron 5 reverse primer	5′-GAA TGT GTA TCT AGC CCA AAG AGA G-3′
FCGR2A H131 forward primer	5′-ATC CCA GAA ATT CTC CCA-3′
FCGR2A R131 forward primer	5′-ATC CCA GAA ATT CTC CCG-3′
FCGR2A common reverse primer	5′-CAA TTT TGC TGC TAT GGG C-3′
HGH-I internal control primer	5′-CAG TGC CTT CCC AAC CAT TCC CTT A-3′
HGH-II internal control primer	5′-ATC CAC TCA CGG ATT TCT GTT GTG TTT C-3′
FCGR3A forward primer	5′-ATA TTT ACA GAA TGG CAC AGG-3′
FCGR3A reverse primer	5′-ACG TGC TGA GCT TGA GTG ATG GTG ATG TTC AC-3′
FCGR3B NA1 forward primer	5′-CAG TGG TTT CAC GTG AA-3′
FCGR3B NA1 reverse primer	5′-ATG GAC TTC TAG CTG CAC CG-3′
FCGR3B NA2 forward primer	5′-CTC AAT GGT ACA GCG TGC TT-3′
FCGR3B NA2 reverse primer	5′-CTG TAC TCT CCA CTG TCG TT-3′
2221 internal control primer	5′-CTT GTG GGT AAA CCA AGG C-3′
2222 internal control primer	5′-TTT GGA AAA ACA CTG AGG TAA GTG GGG GT-3′

univariately with CAL with a P-value < 0·15 were entered in a multivariate logistic regression model to assess their independent prognostic value for CAL. The prognostic values of the variables were expressed as odds ratios (OR) with their 95% confidence intervals (95% CI). The OR can be interpreted as an estimation of the relative risk of CAL. A two-sided P-value < 0·05 was considered statistically significant. All analyses were performed with SPSS for Windows version 11·0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Baseline characteristics are shown in Table 2. In this study 167 Caucasian Dutch children with Kawasaki disease were enrolled. Sufficient clinical and treatment data were available in 159 patients. The boy/girl ratio in this study was 1·8 : 1, which is comparable with the distribution in literature. The median age was 1 year and 10 months, with a range of 32 days 13·5 years. The standard treatment of 2 g/kg IVIG was administered in 149 of the patients (89%). Because of insufficient responsiveness to IVIG, 12 patients (7%) received corticosteroids as additional treatment. In 46 patients (28%) CAL developed during the course of the disease; in eight patients these progressed to giant CAL (diameter > 8 mm). Two patients in our cohort died of the complications of Kawasaki disease.

Table 2. Baseline characteristics.

	No. of patients	
	No.	(%)
Age, median (range)	1 year 10 months (32 days–13·5 years)	
Boys	107	(64%)
CAL	46	(28%)
Giant CAL	8	(5%)

CAL: coronary artery lesions.

Genotype and allelic frequencies

The frequency of the polymorphisms for the various *FCGR* subtypes were compared between children with Kawasaki disease and a healthy control population (Table 3). No difference was found in the distribution of any of the subtypes, nor in the allelic frequencies, when compared to the healthy controls. In addition, all possible combinations of the subtypes were analysed. Again, no difference was found in the distribution of any of the subtypes.

Table 3. *FCGR* genotype frequencies in Kawasaki disease (KD) patients and healthy controls.

Genotype frequency	KD patients	Controls	χ^2	P-value
FcγRIIa	$n = 176$	$n = 239$		
131H/H	55 31 (%)	58 24 (%)	2·65	0·27
131H/R	92 52 (%)	134 56 (%)		
131R/R	29 17 (%)	47 20 (%)		
FcγRIIb	$n = 150$	$n = 239$		
232I/I	122 81 (%)	201 84 (%)	1·05	0·60
232I/T	27 18 (%)	35 15 (%)		
232T/T	1 1 (%)	3 1 (%)		
FcγRIIIa	$n = 172$	$n = 239$		
158F/F	68 40 (%)	99 41 (%)	0·36	0·84
158 V/F	83 48 (%)	115 48 (%)		
158 V/V	21 12 (%)	25 11 (%)		
FcγRIIIb	$n = 176$	$n = 239$		
NA1/NA1	34 19 (%)	34 14 (%)	1·92	0·38
NA1/NA2	80 46 (%)	115 48 (%)		
NA2/NA2	62 35 (%)	90 38 (%)		

Table 4. Univariate analysis for potential risk factors for developing coronary artery lesions in Kawasaki disease.

Factor	*n*	CAL	OR (95% CI)	*P*-value
FcγRIIa				
131H/H	43	12	Ref	
131H/R	75	21	1·01 (0·44–2·32)	0·990
131R/R	24	8	1·29 (0·44–3·80)	0·640
FcγRIIb				
232I/I	100	27	Ref	
232I/T	21	8	1·66 (0·62–4·46)	0·310
232T/T	1	0		
FcγRIIIa				
158F/F	55	17	Ref	
158 V/F	72	19	0·80 (0·37–1·74)	0·580
158 V/V	16	4	0·75 (0·21–2·65)	0·650
FcγRIIIb				
NA1/NA1	29	12	Ref	
NA1/NA2	66	15	0·42 (0·16–1·06)	0·067
NA2/NA2	49	13	0·51 (0·19–1·36)	0·180
Age				
< 1 year	51	23	Ref	
≥ 1 year	104	23	0·35 (0·17–0·71)	0·004
Treatment				
< 10 days	92	21	Ref	
≥ 10 days	44	20	2·82 (1·31–6·07)	0·008

Polymorphisms and other risk factors in relation to CAL

In Table 4 the univariate ORs of CAL associated with the polymorphisms for the *FCGR* genes and two known risk factors are presented. It was shown that age < 1 year and late onset of treatment were statistically significantly associated with an increased risk of CAL. From the *FCGR* genes tested, the *FCGR3B* genotype had a borderline statistically significant influence on the development of CAL. Here the *FCGR3B* genotypes for FcγRIIIb-NA1/NA2 had a slightly decreased risk of CAL compared to those for FcγRIIIb-NA1/NA1. After introduction of the most important univariate associations ($P < 0{\cdot}15$) in a multivariate logistic regression analysis, only the variables age and onset of treatment remained statistically significantly independent risk factors for the development of CAL (age < 1 year: OR 0·36, 95% CI 0·14–0·88; treatment at > 10 days after onset of disease: OR 3·32, 95% CI 13·4–8·19). Although the FCGR3b genotype did not show a significant OR, a trend towards a protective effect was observed (Table 5). No interaction was observed between FCGR3b and onset of treatment on CAL.

Discussion

In this study we evaluated the hypothesis that SNPs for the genes coding for FcγRIIa, IIb, IIIa or IIIb are factors in the susceptibility or pathogenesis in Kawasaki disease. We compared their frequencies because they all have influence either on the binding affinity for the IgG-isotypes of the various activating FcγRs (*FCGR2A*, *FCGR3A* and *FCGR3B*), or on the function of the inhibitory FcγR receptor (*FCGR2B*). We compared the distribution of these SNPs in a cohort of patients with Kawasaki disease with the distribution in a group of healthy Dutch Caucasian controls. It appeared that the distribution of the several allotypes was similar in the patient group when compared to a control population. Besides a borderline significant association for *FCGR3B*, no correlation between SNPs in FcγR genes and the development of CAL was found. The effect of FCGR3B on the risk of CAL appeared not to be confounded by the effect of age and late onset of treatment, as the point estimate of its OR and its 95% CI hardly changed after adjustment for both these variables in a multivariate regression model. Insufficient statistical power may be an explanation for lack of statistical significance. Therefore, an association between FCGR3B and CAL is not necessarily excluded by these results and needs to be explored further in larger numbers.

A recent study described a relationship between the FcγRIIa-131H/R genotype and the coronary outcome in 54 Japanese patients with Kawasaki disease [26]. Racial differences among Japanese and Dutch individuals are known to impact the allele frequency of some of the SNPs in the FcγRs [27]. This could explain the differences between Taniuchi and colleagues' study and ours, although we have tested 59 Japanese patients and 100 controls without finding any change in allele frequency between these two groups (data not shown).

Another study on FcγRs in Kawasaki disease described the regulation of receptor expression on circulating phagocytes in Kawasaki disease [28]. In this study the authors demonstrated an up-regulation of FcγRI and down-regulation of FcγRIII on neutrophils, and concomitant up-regulation of FcγRIII on monocytes. The authors concluded that the expression of FcγRs on circulating phagocytes could be an inflammatory marker of Kawasaki disease. In this study we analysed the association of single SNPs of various well-characterized and functionally relevant SNPs in the genes for

Table 5. Multivariate analysis for risk factors for developing coronary artery lesions in Kawasaki disease.

Factor	*n*	OR (95% CI)	*P*-value
FcγRIIIb			
NA1/NA1	20	Ref	
NA1/NA2	48	0·39 (0·12–1·27)	0·120
NA2/NA2	42	0·57 (0·18–1·82)	0·340
Age			
< 1 year	39	Ref	
≥ 1 year	71	0·36 (0·14–0·88)	0·025
Treatment			
< 10 days	73	Ref	
≥ 10 days	37	3·32 (13·4–8·19)	0·009

FcγRs or possible combinations thereof, with Kawasaki disease or disease severity as defined by the presence or absence of CAL by echocardiography. These SNPs have been associated with disease susceptibility or severity in various infectious diseases caused by, for example, *Neisseria meningitidis* [14,29–31] or *Streptococcus pneumoniae* [15,32,33], as well as in autoimmune disease [17–22,24,25]. As the single inhibitory IgG receptor, the FcγRIIb could seriously impact immunity in this respect. The genotype for the FcγRIIb-232 I/T isoforms represents a SNP in the transmembrane region of the receptor which was found to be important for B cell signalling [12]. Some reports link this receptor to susceptibility to SLE [27], although others have not been able to confirm this in a different racial background [34]. In a recent study, the same *FCGR2B* genotype for FcγRIIb-232 I/T appeared to be a predicting variable for chronic disease in newly diagnosed idiopathic thrombocytopenic purpura in childhood [35]. In Wegener's granulomatosis and in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, associations were also found between polymorphisms in the genes for FcγRs by some groups [22,36] but not by others [23,37].

Although we did not find sufficient evidence for a correlation between the polymorphisms of the genes coding for the several FcγRs and Kawasaki disease, it does not rule out that (one of) these receptors are involved at some point during the disease process or treatment of the disease. The ratio of activating and inhibitory FcγRs on a specific immune cell may be an important factor in the resulting outcome of an immune response, as reported in various experimental animal models in FcγRIIb$^{-/-}$ knock-out mice on inflammation, autoimmunity and an infectious model of *S. pneumoniae* septicaemia [38–40]. The identification of SNPs was performed in genomic DNA. It is hence impossible to investigate the role of transcription or expression factors. Moreover, these factors may differ among the several immune cells involved. Assessing, for example, the expression of the activating and inhibitory FcγRs on the inflammatory cells during several stages of Kawasaki disease might lead to new insights in the role of those receptors in this disease. However, specific antibodies to investigate this issue unequivocally are missing to date and such studies will have to wait for their availability.

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